Parkinson’s Disease

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Overview

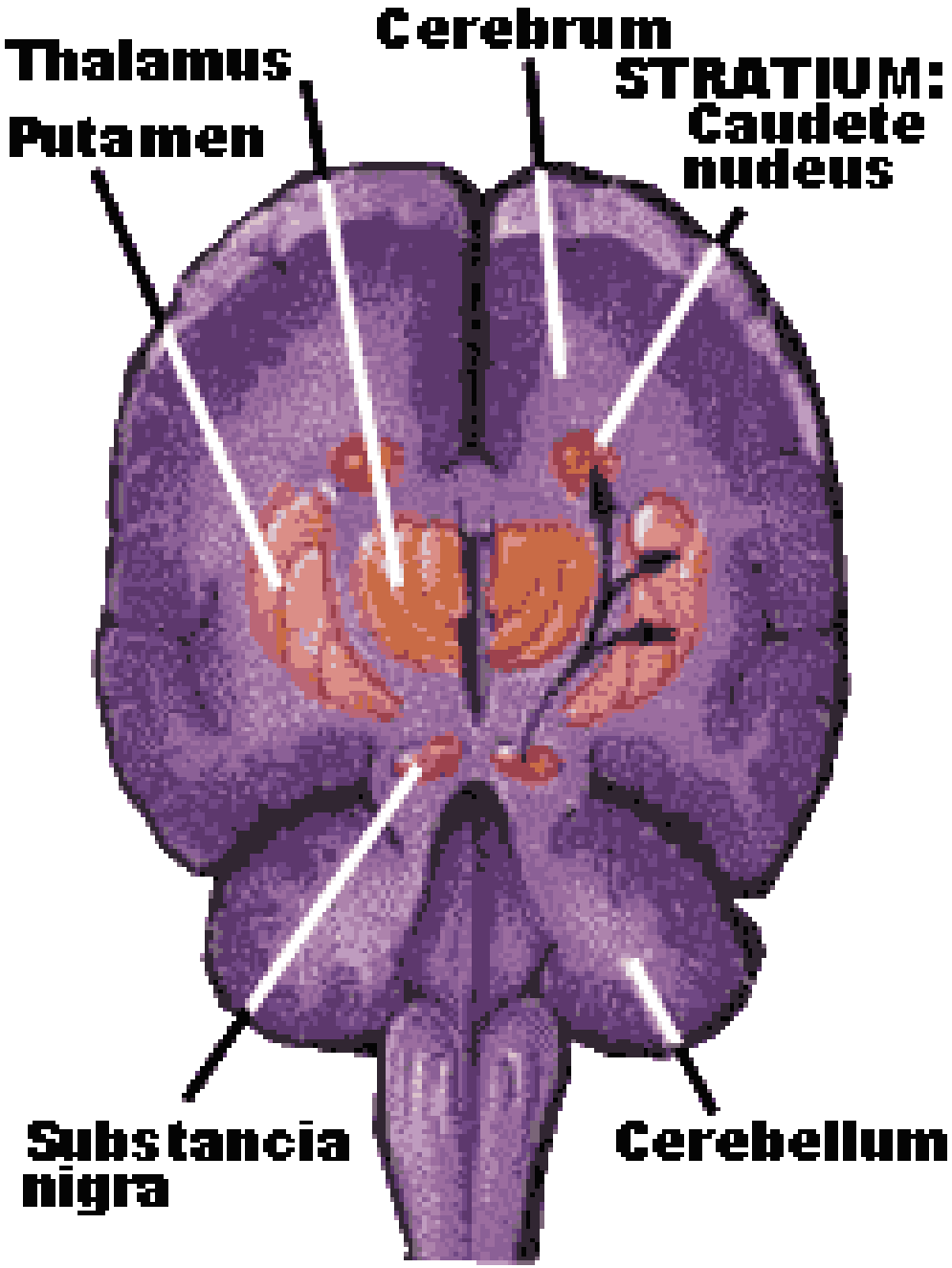
- Epidemiology
- Pathophysiology
- Diagnosis
- Treatment strategies

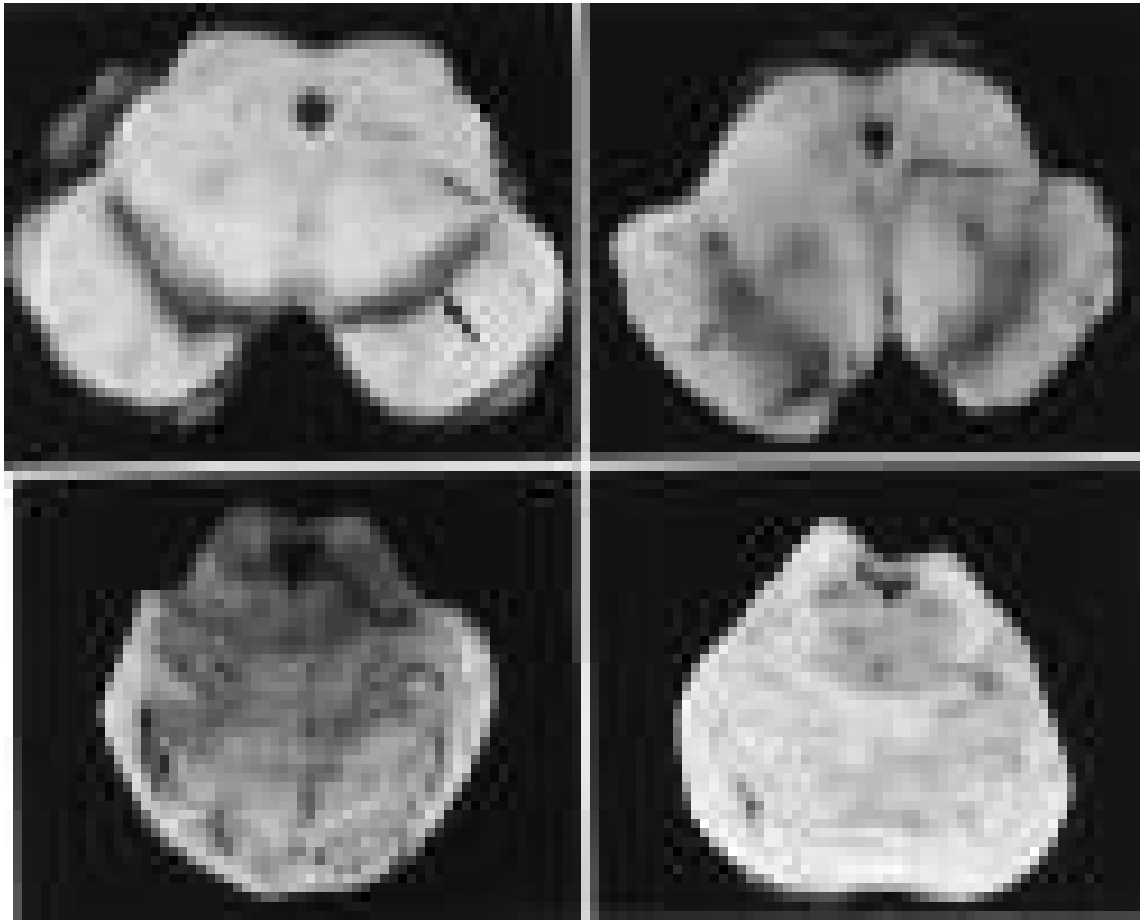
Epidemiology of Parkinson's

- 31 to 328 per 100,000 people worldwide
- Estimated at least 1% of patients over 65yo
- Incidence and prevalence increase with age
- Male:female ratio is 3:2
- Approximately equal ethnic prevalence

Pathophysiology of Parkinson's

- Idiopathic degeneration of dopaminergic neurons in substantia nigra (projects to basal ganglia)
- Basal ganglia lesions result in loss of movement control


Thalamus
Cerebrum
STRATIUM:
Caudete
nudeus
Putamen
Substancia
nigra
Cerebellum



Cardinal Signs of Parkinson's Disease

- Resting tremor
- Cogwheel rigidity
- Bradykinesia
- Postural instability

Symptoms of Parkinson's Disease

- Insidious onset
- "Masked" facies
- Soft, monotonous voice
- Weakness or stiffness
- Resting tremor (pill-rolling)
- Inturning foot (dystonia)
- Anxiety, difficulty sleeping
- Difficulty initiating movements

Physical Exam

- MMSE
- Cranial nerves
- Motor tone
- Muscular strength
- Reflexes
- Coordination
- Sensation
- Cogwheel rigidity
- Postural reflexes– may fall when pushed slightly
- Postural tremor (arms raised)

Differential Diagnosis

- Drug-induced parkinsonism
- Essential tremor
- Multisystem atrophy
- Progressive supranuclear palsy
- Huntington’s Disease
- Normal pressure hydrocephalus
- Multiple lacunar strokes
- Pugilistic (post-traumatic) parkinsonism
- Depression

Workup

- Costly diagnostic workup rarely necessary if history and exam are classic
- CBC, LFT, TSH, ANA, ESR
- CT or MRI
- Neurology or movement disorders specialist consult

Non-Pharmacologic Treatment

- Education of patient and family
- Support psychological and emotional needs
- Regular exercise
- Proper nut

Pharmacologic Treatment Approaches

- Neuroprotective
  - Protect dopaminergic neurons
  - Could be used to slow or stop progression of disease in mild patients and those at genetic risk
  - Increasing research attention

- Symptomatic
  - Use determined by degree of functional impairment
  - Bradykinesia or gait disturbance

Nearly all available treatments are symptomatic and do not appear to significantly alter the natural course of the disease or reverse its progress.

Neuroprotective Therapy

- Selegiline (Eldepryl)
  - Selective MAO-B inhibitor
  - Enhances the effect of L-dopa by slowing its oxidation
  - DATATOP study found delayed progression at 9 months in previously untreated patients receiving 10mg/day
  - Persistent, long-term benefit in slowing progression not yet demonstrated
  - May increase L-dopa-induced side effects of dyskinesia and psychiatric toxicity

Neuroprotective Therapy

- Selegeline recommended dose 5mg BID (AM and noon)
- Lower doses (5mg/day) sufficient to induce MAO-B inhibition
- Higher doses induce nonselective MAO inhibition, may have no additional benefit clinically, and raise risk of hypertensive crises with dietary indiscretions

Symptomatic Therapy

- L-dopa
- Dopamine agonists
- Anticholinergic agents
- Amantadine

L-dopa

- Most effective drug for symptomatic treatment
- Initiate when akinetic symptoms disabling
- Vast majority of patients enjoy response
- Use lowest dose that produces response
  - Usual daily starting dose is 300 to 600 mg

L-Dopa Preparations

- Combined with carbidopa– peripheral decarboxylase inhibitor
- Prevents nausea, vomiting and orthostatic hypotension
- Sinemet

Side Effects of L-Dopa

- Involuntary movements (dyskinesias)
- Abnormal postures of extremities and trunk (dystonias)
- Fluctuations in motor function
- Incidence at least 50% after 5-10yrs of therapy
- Likely due to progressive degeneration of nigrostriatal dopamine terminals, limits normal dopamine uptake and release

Debate over L-dopa

- Motor fluctuations and dyskinesias due to exposure to L-dopa?
- Use of L-dopa hastens formation of free radicals, worsening degeneration?
- No proof L-dopa is directly neurotoxic
- Prospective clinical trial underway to study effects on disease progression

Dopamine Agonists

- Directly stimulate dopamine receptors
  - Ineffective in patients with no therapeutic response to L-dopa
- Ergot dopamine agonists
  - Bromocriptine (Parlodel)
  - Pergolide (Permax)
- Non-ergot dopamine agonists
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)

- Apomorphine and lisuride IV for rescue therapy in sudden akinetic episodes (not approved in US)

Dopamine Agonists

- Do not require peripheral conversion
- Do not compete with amino acid transport
- Do not depend on neuronal uptake and release
- Longer duration of action compared with immediate-release L-dopa
- Side effects nausea, vomiting, orthostatic hypotension, confusion, hallucinations

Dopamine Agonists

- Initially used as adjunct therapy, increasingly studied for earlier use given free-radical concern with L-dopa
- May be neuroprotective by antioxidant effect or reduction of endogenous dopamine turnover
- Prospective, randomized trial comparing L-dopa, dopamine agonists and selegiline is underway

Anticholinergic Drugs

- Dopamine depletion produces cholinergic sensitivity
- Most useful as monotherapy for patients <70yo with disturbing tremor
- Centrally-acting anticholinergic agents
  - Trihexyphenidyl (Artane) and Benztropine (Cogentin)

Anticholinergic Drugs

- Adverse effects common, limit use
- Not for use in elderly
- Memory impairment, confusion, hallucinations
- Dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, tachycardia
- Caution with BPH and closed-angle glaucoma
- Gradual discontinuation to avoid acute exacerbation of parkinsonism

Amantadine

- Antiviral agent with mild antiparkinsonian activity
- Uncertain mechanism
- Increases dopamine release, inhibits dopamine reuptake, stimulates dopamine receptors, may possible exert anticholinergic effects, NMDA receptor antagonist

Amantadine

- Improved akinesia, rigidity and tremor
- Benefit transient for some
- Best used as short-term monotherapy for mild disease
- Little benefit when added to L-dopa, but significant improvement when L-dopa added to amantadine

Amantadine

- Dosed 200 to 300 mg daily
- Renal excretion
- RARE livedo reticularis, ankle edema, confusion, hallucinations, nightmares

Progression of Parkinson's Disease

- Concentration of dopamine becomes more dependent upon plasma L-dopa levels
- "On" and "Off" phenomenon
- Effect of L-dopa begins to wear off in 4 hrs

Alteration of L-dopa Dosing

- Initially increase L-dopa dose
- Shortened dose intervals usually more effective
- Risk of “all or none” response
- Sustained release Sinemet in early stages of wearing off phenomenon

Addition of Second Drug

- Dopamine agonists reduce “off” time, decrease L-dopa doses
- COMT inhibitors more effective extension of L-dopa effect and reduction of “off” time
- Selegeline, MAO-B inhibitor, mildly extends L-dopa effect

Surgery, Implantations and Infusions

- Thalamotomy (unilateral and bilateral)
- Pallidotomy (unilateral and bilateral)
- Deep brain stimulation (DBS)
- Adrenal implant (not recommended)
- Fetal tissue implant (not recommended)
- Growth factor infusion

Other Issues

- Hallucinations
  - Up to 40% of Parkinson's patients
  - Usually visual
  - Associated with severe cognitive decline, daytime somnolence, long duration of illness
  - Best treated with atypical antipsychotics (quetiapine or clozapine)

Other Issues

- Daytime sleepiness
  - common, especially with dopamine agonist use
  - “sleep attacks” also described
  - associated with severity and duration of disease, dose of antiparkinsonian drugs, and worse functional status

Questions?